Guidance for Premarket Notifications for Automated Differential Cell Counters for Immature or Abnormal Blood Cells; Final Guidance for Industry and FDA

Document issued on: November 1, 2000

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Immunology, Hematology and Pathology Branch
Division of Clinical Laboratory Devices
Office of Device Evaluation

Preface

Public Comment

Comments and suggestions may be submitted at any time for Agency consideration to Dockets Management Branch, Division of Management Systems and Policy, Office of Human Resources and Management Services, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD, 20852. When submitting comments, please refer to the exact title of this guidance document. Comments may not be acted upon by the Agency until the document is next revised or updated.

For questions regarding the use or interpretation of this guidance contact Larry J. Brindza at 301-594-1293 or email ljb@cdrh.fda.gov.

Additional Copies

Additional copies are available from the World Wide Web CDRH home page: http://www.fda.gov/cdrh/ode/guidance/1184.pdf or CDRH Facts on Demand at 1-800-899-0381 or 301-827-0111 from a touch-tone telephone. Press 1 to enter the system and enter the document number 1184 followed by the pound sign (#). Follow the remaining voice prompts to complete your request.

Guidance for Premarket Notifications for Automated Differential Cell Counters for Immature or Abnormal Blood Cells

This document is intended to provide guidance. It represents the Agency's current thinking on the above. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

I. Scope:

This guidance document describes a means by which Automated Differential Cell Counter (ADCC) devices may comply with the requirement of special controls for class II devices. Designation of this guidance document as a special control means that manufacturers attempting to establish that their device is substantially equivalent to a predicate ADCC device should demonstrate that the proposed device complies with either the specific recommendations of this guidance or some alternate control that provides equivalent assurances of safety and effectiveness.

The Least Burdensome Approach

The issues identified in this guidance document represent those that we believe need to be addressed before your device can be approved/cleared for marketing. In developing the guidance, we carefully considered the relevant statutory criteria for Agency decision-making. We also considered the burden that may be incurred in your attempt to comply with the guidance and address the issues we have identified. We believe that we have considered the least burdensome approach to resolving the issues presented in the guidance document. If, however, you believe that information is being requested that is not relevant to the regulatory decision for your pending application or that there is a less burdensome way to address the issues, you should follow the procedures outlined in the "A Suggested Approach to Resolving Least Burdensome Issues" document. It is available on our Center webpage at: http://www.fda.gov/cdrh/modact/leastburdensome.html

This guidance applies to ADCC devices as described in the section, Definition of Device.

II. Purpose:

This document is intended to provide guidance on the data and labeling needed by the Center for Devices and Radiological Health (CDRH), Office of Device Evaluation (ODE), to establish safety and effectiveness. Manufacturers desiring to market new ADCC devices or to add new test parameters to legally marketed ADCC devices should contact the Immunology, Hematology, and Pathology Branch to discuss the types of data necessary to support equivalence to a predicate device.

III. Definition of Device:

An automated differential cell counter is a device used to identify one or more of the formed elements of blood. These devices may also have the capability to flag, count, or classify immature or abnormal hematopoietic cells of blood, bone marrow, or other body fluids. These devices may use a combination of an electronic particle counting method, an optical method, or a flow cytometric method utilizing monoclonal cluster designation (CD) markers. The device includes accessory CD markers.

Product Code:	GKZ
Classification:	Class II
Panel:	Hematology and Pathology Devices Panel (81)
Review Required:	Premarket Notification, 510(k)
Regulation:	21 Code of Federal Regulations (CFR) §864.5220 Automated Differential Cell Counter

You should describe the device method or technique, and provide photographs, drawings, and/or schematics sufficient to provide an overview of the technology. As examples, the device technology may include, but is not limited to the following automated methodologies: pattern recognition, optical, fluorescence, flow technology, impedance, cluster analysis, and cytochemistry. You should also include limitations of the method that result from the technology.

Predicate devices for ADCCs must be pre-amendment or cleared devices that have the same or similar intended use(s) as the device being submitted for clearance. The fact that such a predicate may itself be exempt from 510(k*)* requirements does not necessarily exempt ADCCs from this requirement (21 CFR §892.9(b)) since ADCCs may operate using a different fundamental scientific technology than those listed above and, therefore, are not exempt from the requirements for 510(k).

IV. Administrative:

You must meet all the administrative requirements of 21 CFR§807.87, §807.90, and §807.92 or §807.93 for premarket notifications.

You should include information or data on specific performance characteristics, such as accuracy, precision, specificity and sensitivity. The performance characteristics should be related to generally accepted methods using biological specimens from normal and abnormal populations. You should also include a statement summarizing the data upon which the specific performance characteristics are based (21 CFR 809.10 (b)(12)).

As appropriate, you may include references to consensus standards. Additionally, if the test parameter is not already known or well characterized, the data should include valid scientific data with respect to the clinical utility of the reported test parameter. Published journal articles that meet the criteria of 2l CFR 860.7 may be submitted. This information includes a Hazard Analysis and Software Documentation.

V. Instructions for Use:

In addition to meeting the requirements of 21 CFR 809.10, you should provide a concise discussion of the following, as appropriate.

- Clinical indications, significance, and intended use
- A brief historical summary of all test methodologies
- A description of the statistical methods used

Support the statements throughout the both the premarket notification and instructions for use with data or literature citations.

VI. Validation of Specific Performance Characteristics:

All claims for substantial equivalence and specific performance characteristics for using the device should be supported by appropriate data. You should provide summaries of all protocols for testing, and present test data results with analyses and conclusions. You should summarize results and include explanations for unexpected results and any additional testing performed. Charts (scattergrams, histograms, etc.) may be used as part of the analyses and conclusions, when appropriate. We may request laboratory data line listings during our review.

For general guidance, you should follow the International Council for Standardization in Haematology (ICSH) document:

> Guidelines for the evaluation of blood cell analyzers including those used for differential leucocyte and reticulocyte counting and cell marker applications. International Council for Standardization in Haematology: prepared by the ICSH expert panel on cytometry. *Clin Lab Haematol*, 16(2):157-174, 1994.

1. Accuracy

Compare the test parameter(s) to a reference method(s), if available.

You should follow National Committee for Clinical Laboratory Standards (NCCLS) documents:

> *Reference Leukocyte Differential (Proportional) and Evaluation of Instrumental Methods, Approved Standard,* NCCLS document H20-A (ISBN 1-56238-131-8), NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898, 1992.
>
> *Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline*, NCCLS document EP9-A (ISBN 1-56238-283-7), NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898, 1995.

2. Precision

You should follow the NCCLS document:

> *Evaluation of Precision Performance of Clinical Chemistry Devices; Approved Guideline*, NCCLS document EP5-A (ISBN 1-56238-145-8)
> NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898, 1999.

3. Performance

You should provide Performance data, including Clinical Sensitivity and Specificity, for normal and pathological specimens in your premarket notification. You should follow these NCCLS documents in obtaining these data:

> *Reference Leukocyte Differential (Proportional) and Evaluation of Instrumental Methods, Approved Standard,* NCCLS document H20-A, (ISBN 1-56238-131-8), NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898, 1992.
>
> *Preliminary Evaluation of Quantitative Clinical Laboratory Methods, Approved Guideline*, NCCLS document EP 10-A, (ISBN 1-56238-348-5), NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898, 1998.

Assessment of the Clinical Accuracy of Laboratory Tests Using Receiver Operating Characteristic (ROC) Plots, Approved Guideline, NCCLS document GPIO-A, (ISBN 1-56238-285-3), NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898, 1995.

4. Linearity

You should validate the linear range of each measured test parameter with normal and abnormal specimens. We suggest using the following criteria for linearity performance testing:

- The data should fit a linearity regression line.
- The coefficient of determination (r) should be > 0.95.
- You should use a minimum of five dilutions distributed within the linear range.
- The dilution should cover the reportable range for the test parameter.
- Each dilution result should be the mean value of duplicate measurements on the same range.

5. Carryover

Where applicable, you should provide carryover data from high to low specimens. Analyze a high specimen three consecutive times followed by a low specimen three consecutive times. You should follow the ICSH document:

Guidelines for the evaluation of blood cell analyzers including those used for differential leucocyte and reticulocyte counting and cell marker applications. International Council for Standardization in Haematology: prepared by the ICSH expert panel on cytometry. *Clin Lab Haematol*, 16(2):157-174, 1994.

6. Background

Where applicable, you should state the method used to perform the test and the test characteristic obtained. State the background result for the method/technology used.

7. Limitations of the Procedure

Include a statement of the limitations of the procedure. State known extrinsic factors or interfering substances affecting results. If more specific or more sensitive testing is indicated, the need for additional test(s) should be stated.

8. Specimens

Where appropriate, you should provide the type of anticoagulants, age, storage conditions, etc. You should follow the NCCLS document:

Procedures for the Collection of Diagnostic Blood Specimens by Skin Puncture; Approved Standard--Fourth Edition, NCCLS document H4-A4, (ISBN 1-56238-111-9), NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898, 1999.

You should also follow the ICSH document, where applicable:

Recommendations of the International Council for Standardization in Haematology for ethylenediaminetetraacetic acid anticoagulation of blood for blood cell counting and sizing. *Am J Clin Path,* 100(4)371-372, 1993.

9. Reference Values

You should include a description of the approach taken to interpret the observed values. When appropriate, distinguish between clinical and statistical significance.

You should follow the ICSH/International Federation of Clinical Chemistry (IFCC) documents:

IFCC and ICSH: Approved recommendation (1986) on the Theory of Reference Values. Part 1. The concept of reference values. *J Clin Chem Clin Biochem*, 25:337-342, 1987.

IFCC and ICSH: Approved recommendation (1987) on the Theory of Reference Values. Part 5. Statistical treatment of collected reference values. Determination of reference limits. *J Clin Chem Clin Biochem*, 25:645-656, 1987.

IFCC and ICSH: Approved recommendation (1987) on the Theory of Reference Values. Part 6. Presentation of observed values related to reference values. *J Clin Chem Clin Biochem*, 25:657-662, 1987.

You should also follow the NCCLS document:

How to Define and Determine Reference Intervals in the Clinical Laboratory; Approved Guideline—Second Edition, NCCLS document C28-A2, (ISBN P56238-269-I), NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898, 2000.